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Could platelet mass index (PMI) be a new prognostic biomarker for COVİD-19?

Platelet mass index be a new COVID-19 prognostic biomarker

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Abstract
Aim: Although most patients with COVID-19 experience respiratory tract infections, severe reactions to the virus may cause coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation and thrombotic microangiopathy. Fluctuations in platelet markers, which are an indicator of the acute phase response for COVID-19, are of clinical importance. The aim of this study is to evaluate the relationship between disease severity and Platelet Mass Index (MPI) parameters in COVID-19 patients.
Material and Methods: This retrospective observational study was conducted with patients who were diagnosed with COVID-19 in a tertiary hospital. The study was continued with the remaining 280 patients. All laboratory data were scanned retrospectively from patient files and hospital information system.
Results: A very high positive correlation was found between PMI and PLT. The PMI value in women was significantly higher than in men. It was observed that PMI did not differ significantly in terms of mortality, intubation, CPAP and comorbidity. PMI vs. Pneumonia Ct Severity Score, biochemistry parameters (AST, CRP), hemogram parameters (WBC, HGB, HCT, MCV, LYM, MPV EO) and coagulation factors (aPTT and FIB) at various levels of positive/negative, weak and strong, and significant relationship was found. There was no significant relationship between hormone and D-dimer when compared with PMI.
Discussion: Although platelet count alone does not provide information about the prognosis of the disease, PMI may guide the clinician as an indicator of lung damage in seriously ill patients

Keywords
COVID-19, PMI, Biomarker

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Introduction

Although most patients with COVID-19 develop a respiratory tract infection, many patients with severe cases present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy [1]. The prevalence of COVID-19 coagulation abnormalities is rising as more patients develop venous and arterial thromboembolic complications that may go unrecognized [2]. An acute-phase reaction can lead to an increase in platelet count during the inflammation process as part of the natural immune response [3]. Hospitalized patients with newly confirmed or presumptive COVID-19 infections should be tested for coagulation on admission, including D-dimer, prothrombin (PT), activated partial thromboplastin time (aPTT), fibrinogen, and platelet count, as these tests can provide useful prognostic information [4].

Evidence of abnormal coagulation parameters associated with COVID-19 appeared in early reports from China: baseline characteristics of the first 99 patients hospitalized in Wuhan indicated that 6% had an elevated aPTT, 5% had elevated PT, 36% had elevated D-dimer and increased biomarkers of inflammation, including interleukin-6 (IL-6), erythrocyte sedimentation rate, and C-reactive protein (CRP) [4]. Thrombocytopenia occurred in only 12% of patients; however, 5 (5%) patients developed other coinfections (1 bacterial, 4 fungal) and 4 (4%) developed septic shock [5]. Considering the lack of consensus on the use of prophylactic anticoagulants, a biomarker is particularly important for COVID-19 patients with elevated D-dimer levels, but without known thrombotic complications [6]. Nowadays, both platelet count and platelet size can be easily measured using automatic counting devices; however, only a few studies have evaluated the clinical importance of using fluctuations in platelet counts as an indicator of acute-phase response [7].

The aim of this study is to define the platelet mass index (PMI), which includes both platelet count and platelet volume and is an important indicator of platelet activity [8]. This study is also intended to provide guidance for clinicians in determining the need for prophylactic anticoagulants.

Material and Methods

The medical records of 280 patients diagnosed with COVID-19 following a real-time PCR (RT-PCR) test who were treated at the Mehmet Akif Inan Education and Research Hospital, Sanlıurfa, Turkey, between April 2020 and December 2020 were reviewed. This study was approved by the Ethics Committee of the Mehmet Akif Inan Education and Research Hospital and the Turkish Ministry of Health (HRU/21.06).

RT-PCR results, routine hemograms, and biochemical data of all patients treated in any clinic in our hospital who tested positive for COVID-19 were obtained from the hospital system. The patients' hemogram parameters were measured automatically using a Sysmex xn1000 (Sysmex Inc., Japan). Biochemistry-Hormone-D-Dimer analysis Roche Cobas 8000. Coagulation was measured automatically with Sysmex cs2500 devices (Sysmex Inc., Japan).

PMI was calculated by multiplying the platelet count by the mean platelet volume (MPV):PMI = platelet count × MPV/103(fL/nL) [8].

All chest CT images were analyzed by a radiologist without access to clinical or laboratory findings, based on previously published studies of COVID-19 [9,10],

The 280 patients were divided into 3 groups, which were based on the clinical stages of COVID-19 defined by China's Health Authority and the interim guidance of the World Health Organization: ordinary cases, severe cases, and critical cases [11, 12].

Statistics

The evaluation of the data was made with the SPSS 21.00 program. Descriptive statistics were used

Results

In total, 280 patients were included in the study. One hundred twenty- six (45.3%) of the patients were women, 152 (54.7%) were men. One hundred seventy-nine (64.4%) patients had additional diseases such as hypertension, diabetes, COPD (Chronic obstructive pulmonary disease). The ranges of biochemistry of patients, hormones, coagulation results are shown in Table 1. The age, hospitalization period of the patients included in the study ranged from 17 to 98, and the mean age was calculated as 60.4±17.2 years, between 1 and 42 days and the mean hospitalization period was 9.66±6.78 days, respectively.

According to the respiratory support status of the patients, 64 (23%) were intubated and 72 (25%) were using CPAP (Continuous Positive Airway Pressure). The pneumonia CT severity score of the patients was between 0-20 and the mean score was found to be 7.67±4.9.

Table 1. Value of patients' biochemistry, hormone, coagulation results and correlation analysis of PMI

	Median±SD	PMI*	
		r	p
AST (U/L)	42.6±42.5	-0.12	0.04
CRP (mg/L)	92.0±89.1	0.12	0.05
Procalcitonin (ng/ml)	2.0±9.3	0.00	0.10
Ferritin (ng/ml)	758.7±766.3	-0.08	0.26
CK-MB (ng/ml)	2.6±4.8	0.04	0.55
Troponin (ng/mL)	35.9±141.1	0.01	0.91
WBC (103/µL)	11.2±18.5	0.36	0.00
RBC (106/µL)	4.6±0.74	-0.03	0.59
HGB (g/dL)	12.9±2.1	-0.16	0.01
HCT (%)	39.1±5.8	-0.13	0.04
MCV (fL)	84.9±7.0	-0.13	0.04
LYM (103/µL)	18.8±22.0	-0.14	0.02
EO (103/µL)	0.65±2.7	0.10	0.09
PLT (103/µL)	231.1±92.8	0.97	0.00
MPV (fL)	10.6±0.9	-0.18	0.01
PT (sec)	13.3±4.5	-0.05	0.39
INR (%)	1.1±0.4	-0.05	0.38
aPTT (sec)	30.1±13.1	-0.14	0.03
Fibrinogen (mg/dL)	4.9±1.9	0.26	0.00
D-dimer (mg/L)	1.5±2.3	0.11	0.07

* Correlation of PMI with biochemical and hormone hemogram coagulation parameters r<0.2 Very weak correlation or no correlation, 0.2-0.4 Weak correlation, 0.4-0.6 Moderate correlation, 0.6-08 High correlation,> 0.8 it is interpreted that there is a very high correlation.

Table 2. Correlation of PMI with gender, mortality, intubation, CPAP and comorbidity

		MPI	P
Gender	Women	2603.2±95	0.007*
	Men	2307.3±82	
Mortality	Yes	2447.4±87	0.785
	No	2415.2±93	
Intubation	Yes	2432.1±86	0.855
	No	2455.7±97	
CPAP	Yes	2426.3±92	0.727
	No	2469.9±81	
Comorbidity	Yes	2374.1±82	0.385
	No	2472.9±93	

Median ± Standard deviation (SD) was used for presenting data.
* Statistically significant difference.

Table 3. Correlation of PMI with age, hospitalization days, clinical severity score and pneumonia Ct severity score

		PMI	Age	Hospitalization days	Pneumonia Ct Severity Score	Clinical Severity Score
PMI	r	1.00				
	p	-				
Age	r	-0.03	1.00			
	p	0,61	-			
Hospitalization days	r	-0.07	0.10	1.00		
	p	0.27	0.10	-		
Pneumonia Ct Severity Score	r	0.24	0.17	0.15	1.00	
	p	0.00	0.01	0.01	-	
Clinical Severity Score	r	0.05	0.38	0.18	0.70	1.00
	p	0.44	0.00	0.01	0.00	-

When patients were examined according to their clinical severity score, it was seen that were 7.6% "Mild", 55% "Common", 33.8% "Severe" and 3.6% "Critical".

PMI value in women is significantly higher than in men ($p < 0.05$). It has been observed that PMI does not differ significantly in terms of mortality, intubation, CPAP and comorbidity (Table 2).

As a result of the study, a positive, weak and significant relationship was found between PMI and Pneumonia Ct Severity Score ($r=0.237$; $p<0.001$). It was observed that there was no significant relationship between age, day of hospitalization, Clinical Severity Score and PMI ($p>0.05$) (Table 3)

For biochemical parameters: a negative, very weak and significant relationship between PMI and AST ($r=-0.124$; $p=0.043$) was found; A positive, very weak and significant relationship ($r=0.123$; $p=0.045$) was found between PMI and CRP (Table 1). There was no significant relationship between PMI and hormone results (Table 1).

For hemogram parameters: a positive, weak and significant relationship between PMI and WBC was found, ($r=0.35$); a negative, very weak ($r<0.2$) and significant relationship ($p<0.05$) between PMI and HGB, HCT, MCV, LYM and MPV was found; a positive, very weak significant relationship between PMI and EO, ($r=0.13$; $p<0.05$) was found; A very high ($r=0.970$; $p<0.001$) positive correlation was found between PMI and PLT (Table 1).

For the coagulation parameter: a negative, very weak and significant relationship between aPTT and PMI ($r=-0.139$; $p<0.05$) was found; A positive, weak and significant relationship was found between PMI and FIB. ($r=0.26$, $p<0.001$) (Table 1). There was no significant relationship between PMI and D-dimer (Table 1).

Discussion

COVID-19 is most commonly associated with ARDS and hypoxemic respiratory failure [13]. Furthermore, thrombosis, including pulmonary embolism, venous thrombosis, and ischemic stroke, are common among severely ill patients [13]. Significant derangements in the coagulation cascade have been observed in critically ill COVID-19 patients, including elevated D-dimers, a relatively modest decrease in platelet count, and a prolongation of the prothrombin time [14]. Recent postmortem evaluation of COVID-19 patients has demonstrated severe endothelial injury with cellular death/apoptosis, and the presence of intracellular virus in the autopsy lung with thrombosis and small to middle-size pulmonary vessels. Clotting and vascular damage were also conformed in the alveolar capillary in COVID-19 [15]. In our study, it was observed that PMI was lower in the mortality group, but the difference between the groups was not statistically significant ($p>0.05$), and we found that PMI is correlated with the Pulmonary Ct Score. PMI may be a marker for lung injury.

In COVID-19 disease, there are two types of coagulation problems. One of them is that COVID-19 infection produces a prominent elevation of fibrinogen and D-dimer/fibrinogen degradation products. This is associated with systemic hyper coagulability and frequent venous thromboembolic events (VTE). COVID-19 also leads to arterial thrombotic events (including strokes and ischemic limbs), as well as microvascular thrombotic disorders (as frequently documented at autopsy in the pulmonary vascular beds). COVID-19 patients often have mild thrombocytopenia and appear to have increased platelet consumption, together with a corresponding increase in platelet production [16]. Here, in our study, the fact that PMI was not correlated with D-dimer, patient age, comorbidities, and hospital stay, but was compatible with Pneumonia Ct Score, concluded that PMI may be an early marker of lung damage associated with arterial angiopathy rather than systemic hyper coagulability and VTE. However, PMI's correlation with aPTT and fibrinogen suggests that it is also an indescribable indicator for systemic coagulation

In meta-analysis made, COVID-19 patients revealed that patients with severe disease had lower platelet counts than those with non-severe disease. According to this, the non-survivors had a much lower platelet count than the survivors [17]. In our study, positive correlation with PMI and platelet counts may be important in diagnosing patients with severe lung damage before entering the DIC period.

Although viral infection can be associated with thrombocytopenia due to a variety of causes [18], in a study by Yin et al, those with COVID-19 disease actually had high platelet counts compared to patients with severe pneumonia but without COVID-19, [19]. Some studies have shown there are significant intravascular platelet aggregates in COVID-19 autopsy lung specimens, located primarily in the inter alveolar capillaries and smaller vessels; the degree of platelet deposition is not more than is seen in other fatal pulmonary infections.

However, none of the COVID-19 patients assessed in their study were thrombocytopenic [16]. In our study, we did not find a low number of platelets in severe COVID-19 patients (Table 1, Mean/std deviation; 231,1±92.8). Although the platelet count alone does not provide information about the prognosis of the disease, PMI may guide the clinician as an indicator of lung damage in seriously ill patients.

PMI is calculated in automated hemogram devices; it should be kept in mind that it can be used in routine follow-up.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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